UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte STEPHEN ANDERSON, GAETANO MONTELIONE and YUANPENG HUANG

Appeal No. 2005-0761
Application No. 09/744,002

ON BRIEF

Before ELLIS, SCHEINER, and MILLS, Administrative Patent Judges.

ELLIS, Administrative Patent Judge.

DECISION ON APPEAL

This is an appeal pursuant to 35 U.S.C. § 134 from the examiner's final rejection of claims 1-13, all the claims pending in the application.

As a preliminary matter we note the appellants' statement on page 4 of the Brief that the claims stand or fall together. Accordingly, for purposes of this appeal we will consider the issues as they apply to claim 1, which is representative of the subject matter rejected under 35 U.S.C. § 103(a); and claim 12, the only claim rejected under 35 U.S.C. § 102(b).

Claims 1 and 12 read as follows:[1]

1. A high-throughput method for determining the biochemical function of a protein or polypeptide domain of unknown function comprising:

(A) identifying a putative polypeptide domain that properly folds into a stable polypeptide domain, said stable polypeptide domain having a defined three dimensional structure;

(B) determining [the] three dimensional structure of the stable polypeptide domain from an automated analysis of NMR spectrometer spectra of said polypeptide domain, wherein said automated analysis is conducted by a NOESY-Assign process;

(C) comparing the determined three dimensional structure of the stable polypeptide domain to known three-dimensional structures in a protein data bank, wherein said comparison identifies known structures within said protein data bank that are homologous to the determined three dimensional structure; and

(D) correlating a biochemical function corresponding to the identified homologous structure to a biochemical function for the stable polypeptide domain.

12. An integrated system for rapid determination of a biochemical function of a protein or protein domain of unknown function:

(A) a first computer algorithm capable of parsing said target polynucleotide into at least one putative domain encoding region;

(B) a designated lab for expressing said putative domain;

(C) an NMR spectrometer for determining individual spin resonances of amino acids of said putative domain;

---

[1] We note that after the examiner's final rejection of the claims, the appellants filed a proposed amendment to claims 1, 12 and 13 (attached to the Brief). The examiner has indicated that the amendment was not entered. Answer, p. 2. Accordingly, we have not considered the amended claims.

(D) a data collection device capable of collecting NMR spectral data, wherein said data collection device is operatively coupled to said NMR spectrometer;

(E) at least one computer;

(F) a second computer algorithm capable of assigning individual spin resonances to individual amino acids of a polypeptide;

(G) a third computer algorithm capable of determining tertiary structure of a polypeptide, wherein said polypeptide has had resonances assigned to individual amino acids of said polypeptide;

(H) a database, wherein stored within said database is information about the structure and function of known proteins and determined proteins; and

(I) a fourth computer algorithm capable of determining 3D structure homology between the determined three dimensional structure of a polypeptide of unknown function to three dimensional structure of a protein of known function, wherein said protein of known structure is stored within said protein database, wherein said fourth computer algorithm determines said structure by an automated NOESY-Assign process.

The references relied upon by the examiner are:

Mumenthaler et al. (Mumenthaler), "Automated assignment of simulated and experimental NOSEY spectra of proteins by feedback filtering and self correcting distance geometry," J. Mol. Biology, vol. 254, pp. 465-480 (1995).

Wallace, et al. (Wallace), "Derivation of 3D coordinate templates for searching structural databases: Application to Ser-His-Asp catalytic triads in the serine proteases and lipases," Protein Science, vol. 5, pp. 1001-1013 (1996).

Faber et al. (Faber), "Determination of eukaryotic protein coding regions using neural networks and information theory," J. Mol. Biology, vol. 226, pp. 471-479 (1992).

Friedrichs et al. (Friedrichs), "An automated procedure for the assignment of protein ^{1}HN, ^{15}N, $^{13}C^{\alpha}$, $^{1}H^{\alpha}$, $^{13}C^{\beta}$, and $^{1}H^{\beta}$ resonances," Journal of Biomolecular NMR, vol. 4, pp. 703-726 (1994).

Holm et al. (Holm), "DALI: A network tool for protein structure comparison," Trends in Biotechnol., vol. 85, pp. 478-480 (1995).

Bagby et al. (Bagby), "The button test: A small scale method using microdialysis cells for assessing protein solubility at concentrations suitable for NMR," Journal of Biomolecular NMR, vol. 10, pp. 279-282 (1997).

The claims stand rejected as follows:

I. Claim 12 stands rejected under 35 U.S.C. § 102(b) as being anticipated by the University of Texas at Galveston campus as evidenced by Mumenthaler.[2]

---

[2] We note that the appellants and the examiner have raised the issue of what is the effective filing date of the claimed subject matter. This is not an appealable matter. Benefit of an earlier-filed application as to the subject matter of the claims of a continuation-in-part application only arises when there is an issue of patentability involving a viable intervening reference. In re Gostelli, 872 F.2d 1008, 1010-1011, 10 USPQ2d 1614, 1616 (Fed. Cir. 1989). This is not the case here because all of the applied prior art predates the October 29, 1998 filing date of the parent Application No. 09/181,601.

For purposes of clarification, we point out, that in order to obtain the benefit of the filing date of an earlier-filed application under 35 U.S.C. § 120, each application in the chain must comply with the written description requirement of 35 U.S.C. § 112, first paragraph. Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1571, 41 USPQ2d 1961, 1965-66 (Fed. Cir. 1997); In re van Langenhoven, 458 F.2d 132, 136, 173 USPQ 426, 429 (CCPA 1972). However, as stated in the M.P.E.P. § 2133.01:

> When applicant files a continuation-in-part whose claims are not supported by the parent application, the effective filing date is the filing date of the child CIP. Any prior art disclosing the invention or an obvious variant thereof having a critical reference date more than 1 year prior to the filing date of the child will bar the issuance of a patent under 35 U.S.C. 102(b). Paperless Accounting v. Bay Area Rapid Transit System, 804 F.2d 659, 665, 231 USPQ 649, 653 (Fed. Cir 1986) [emphasis added].

Since the present claims recite a limitation which was not supported by a proper disclosure under 35 U.S.C. § 112, first paragraph, in the parent application, they are only entitled to the August 2, 2001 filing date of the continuation-in-part application (Application No. 09/744,002). In re Langenhoven, 458 F.2d at 136, 173 USPQ at 429. Thus, in the event of future prosecution of the application, the examiner may wish to determine whether there are any pertinent intervening references.

II. Claims 1, 5 and 11 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Wallace and Mumenthaler.

III. Claims 1-5 and 11 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Wallace, Mumenthaler and Farber.

IV. Claims 1, 5, 6 and 11 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Wallace, Mumenthaler and Friedrichs.

V. Claims 1, 5, 7 and 11 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Wallace, Mumenthaler and Bagby.

VI. Claims 1, 5 and 8-11 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Wallace, Mumenthaler and Holm.

VII. Claims 1, 5, 8-11 and 13 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Wallace, Mumenthaler, Holm and Farber.

We reverse Rejection I and affirm Rejections II-IV.

Background

As indicated by claim 1, above, the present invention is directed to a "high-throughput" method of determining the function of a protein and protein domains by examining their three dimensional (3-D) structure.

It is well known that a protein's tertiary structure is determined by its primary (amino acid) sequence. Specification, p. 2. The tertiary structure or folding of the protein results in one or more autonomous units known as domains. Id., p. 3.

Multidomain proteins in higher organisms are said to be encoded by genes containing multiple exons. Id.

The specification discloses that several techniques were known in the art for determining the three dimensional structure of a protein molecule such as X-ray crystallography and Nuclear Magnetic Resonance (NMR).[3] Specification, p. 3. According to the specification, it was rare for prior investigators to determine the three dimensional structure of a protein before its biochemical function was determined by

---

[3] The specification summarizes (on pages 4-5) Wüthrich's (Wüthrich, Science, vol. 243, pp. 45-50 (1989)) classical approach for the analysis of NMR resonance assignments as follows:

> Step 1: Identification of individual resonances associated with each spin system, and designation of key atom types (e.g., H^N, H^α, N, C^α, C^β, etc.).
>
> Step 2: Classification of each identified spin system with respect to one or more possible amino acid residue type(s).
>
> Step 3: Identification of possible sequential relations between spin systems using inter-residue NOESY or triple-resonance data.
>
> Step 4: Unique mapping of strings of sequentially-connected spin systems to segments of the amino acid sequence, thus establishing "sequence specific assignments."
>
> Step 5: Extension of assignments to resonances of peripheral side-chain nuclei in each spin system, and determination of stereospecific assignments.
>
> Step 6: Generation of distance constraints using assigned resonance frequencies to interpret NOESY, scalar-coupling, and hydrogen/deuterium-exchange data in terms of "sequence-specific distance constraints."
>
> Step 7: Structure generation using these constraints.

other methods. Id., p. 5. The present invention is said to differ from past research methods because it provides a means of first determining the three dimensional structure of a protein whose function is unknown and using this structure to determine its function. Id.

With respect to the term "high-throughput" the specification states that one skilled in the art is currently able to determine the three dimensional structure of only one protein per year. Specification, p. 27. According to the specification, the claimed invention would "enable a properly equipped laboratory to generate the 3-D structure of one protein per month per NMR machine." Id. Thus, a "high-throughput" method is said to refer "the ability to determine the 3D structures of protein domains of unknown function at a rate which is faster than the rate at which a skilled artisan could determine a protein structure using traditional methodologies." Id.

Discussion

Rejection I - 35 U.S.C. § 102(b)

The examiner argues that

> . . . The University of Texas at Galveston campus comprised a computer, an NMR facility which had a spectrometer, data collection device, and computer algorithms to analyze the NMR spectra and determine the tertiary structure of the proteins including the NOAH program for automated assignment of NOESY spectra, as well as laboratories for expressing proteins, access to the Wisconsin programs which can parse target polynucleotides, and internet access to the Protein Data Bank and the DALI webserver [Answer, p. 4].

It is well established that anticipation requires that each and every limitation set forth in a claim be present, either expressly or inherently, in a single prior art reference. In re Robertson, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950 (Fed. Cir. 1999); Celeritas Techs. Ltd. v. Rockwell Int'l Corp., 150 F.3d 1354, 1360, 47 USPQ2d 1516, 1522 (Fed. Cir. 1998); Verdegaal Bros., Inc. v. Union Oil Co., 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987); Lindemann Maschinenfabrik GMBH v. American Hoist and Derrick Co., 730 F.2d 1452, 1458, 221 USPQ 481, 485 (Fed. Cir. 1984).

Here, we find that the examiner appears to recognize that claim 12 is simply directed to a series of components; e.g., a computer capable of identifying a polynucleotide having at least one putative domain encoding region; a laboratory that can express said putative domain, etc., because it lacks a phrase which ties the components set forth in subparts (A)- (I) together. That is, the claim is not directed to an integrated system which "comprises" or "consists of" the aforementioned components. Thus, as we understand it, the examiner's position is that because the University of Texas is able to perform the method of automatically assigning proton-proton NOESY spectra and calculating the three dimensional structure of a protein from NMR, as evidenced by Mumenthaler, the university must have each of the individual components set forth in claim 12 in various locations on its Galveston campus.

We remind the examiner that anticipation cannot be established based on probability or possibility. See, In re Robertson, 169 F.3d 743, 745, 49 USQP2d 1949, 1951, (Fed. Cir. 1999); In re Oelrich, 666 F.2d 578, 581, 212 USPQ 323, 326 (CCPA

1981) quoting Hansgirg v. Kemmer, 102 F.2d 212, 214, 40 USPQ 665, 667 (CCPA 1939)(" the mere fact that a certain thing may result from a given set of circumstances is not sufficient"). Here, the examiner has not pointed to any section(s) in Mumenthaler which teach (i) a lab for expressing the putative domain of an unknown protein as set forth in subpart (B); (ii) a database as recited in subpart (H); and (iii) a fourth computer as required by subpart (I), of claim 12. As highly likely as it may be that the university does in fact have the referenced laboratory, database and computer, we remind the examiner that an anticipation rejection must be based on substantive evidence, not speculation. Since we do not find, and the examiner has not pointed out, any teachings in Mumenthaler of a laboratory for expressing protein domains (B), a database which stores the structure and function of known proteins (H), and a computer capable of determining the structural homology between the three dimensional structure of an unknown protein and a known protein (I), we do not find that it [Mumenthaler] anticipates the subject matter of claim 12.

Accordingly, Rejection I is reversed.

Rejections II-VII - 35 U.S.C. § 103(a)

As discussed above, the appellants state that the claims stand or fall together. Thus, we have considered the issues as they apply to representative claim 1. Since in all the § 103 rejections, claim 1 is said to be unpatentable over the Wallace and Mumenthaler references, we have primarily limited our consideration of the issues

accordingly. That is, if claim 1 falls over the teachings of the two aforementioned references, all the claims fall in each of the obviousness rejections.

With respect to the applied prior art, we find that Wallace discloses that databases such as PROSITE are well known for identifying the biological function and tertiary (3-D) structure for unknown protein sequences. Wallace, the abstract, p. 1001, col. 1, para. 1. Wallace further discloses that the PROSITE database information, in combination with automatic sequence alignment algorithms, enables swift assessment of an unknown protein sequences. Id.

Wallace still further discloses a method for automatically deriving the 3-D structure of the proteins deposited in the Brookhaven Protein Data Bank (PDB). Wallace, the abstract. Wallace still further discloses that "the development of databases of 3D templates, such as those that currently exist for protein sequence templates, will help identify the functions of new protein structures as they are determined and pinpoint their functionally important regions." Id. Wallace exemplifies its method using the Ser-His-Asp catalytic triad found in serine proteases and triacylglycerol lipases. Id., pp. 1004-1005. To that end, Wallace discloses the generation of 3-D coordinate templates by first extracting all occurrences of interacting Ser, His and Asp residues, catalytic and noncatalytic, irrespective of conformation from the protein data bank (PDB). Id., p. 1004. Wallace further discloses distinguishing those Ser-His-Asp triplets that are catalytic triads with well-conserved

conformations to form the basis for calculating a final 3-D template known as the functional template. Id. Wallace still further discloses that the functional 3-D template was employed to identify other Ser-His-Asp catalytic triads in the PDB as opposed to noncatalytic triads. Id., p. 1009, col. 2. Wallace still further discloses correlating the biochemical function of the newly-identified triads with the biochemical function of the functional consensus Ser-His-Asp template. Id., Figure 5.

In view of these results, Wallace concludes that "[a]s the number of known protein structures increases, so the need for a 3D equivalent of PROSITE grows with it-especially for identifying likely functions of proteins whose biological role is unknown and, equally usefully, for locating the functional regions and residues involved." Wallace, p. 1001, cols. 1-2.

As to Mumenthaler, we find that the publication discloses a "method for automatically assigning proton-proton NOESY spectra" for the automatic calculation of three-dimensional protein structures from NMR spectra. Mumenthaler, e.g., the abstract.

The examiner argues that it would have been obvious to one of ordinary skill in the art

> to combine the 3-D structural alignment and function determination method of Wallace with the NOESY assignment method of Mumenthaler since Mumenthaler states "We regard our method as a highly practical tool for automatic calculation of three dimensional protein structures from NMR spectra with minimal human interference (abstract)." [Answer, p. 6].

The examiner further argues that one of ordinary skill in the art would have been motivated to determine the 3D structures disclosed by Wallace using the automated NOESY method of Mumenthaler since said method [NOESY] is a highly practical tool which requires less work (Mumenthaler, p. 4366, col. 2). Id.

In response, the appellants argue that Wallace does not teach or suggest an essential step recited in the claimed method; viz., "the identification of a protein or polypeptide domain that properly folds into a stable polypeptide domain with a defined three dimensional structure." Brief, pp. 14-15. The appellants contend that Wallace only discloses the "derivation of 3-dimensional coordinate templates that have been derived from known three dimensional structures." Id., p. 15. The appellants further argue that Wallace discloses the identification of a specific triad of amino acids that form a domain and thus the "domain concept" taught by publication "is completely different from the structural domain concept taught in the instant application." Id. The appellants still further argue that Wallace "is limited to teaching a skilled artisan that databases may be searched using a specific 3D template, the triad, and then used to identify a potential biological function of a protein with an unknown structure." Id., p. 16. We find these arguments unpersuasive.

It is well established that the examiner has the initial burden under § 103 to establish a prima facie case of obviousness. In re Oetiker, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992); In re Piasecki, 745 F.2d 1468, 1471-72, 223 USPQ 785, 787-88 (Fed. Cir. 1984). It is the examiner's responsibility to show that

some objective teaching or suggestion in the applied prior art, or knowledge generally available [in the art] would have led one of ordinary skill in the art to combine the references to arrive at the claimed invention. Pro-Mold & Tool Co. v. Great Lakes Plastics, Inc., 75 F.3d 1568, 1573, 37 USPQ2d 1626, 1629 (Fed. Cir. 1996). This the examiner has done. Our reasons for affirming the obviousness rejections follow.

First, as pointed out by the examiner, and evinced by Wallace and Mumenthaler, the claimed method is directed to a series of steps routinely performed in biotechnology. DNA sequences are routinely isolated and analyzed to identify those regions therein which encode proteins. See, e.g., Farber, of record, and the specification, pp. 10-11. After a protein coding region is identified, it is then analyzed to determine its 3-D conformation and biological function. See, Wallace, the abstract and Mumenthaler. Wallace discloses the determination of the three dimensional structure of a protein domain of known function and suggests the development of databases with three dimensional domains to identify the function of unknown proteins. Wallace, the abstract. Thus, we find that Wallace discloses each of the steps set forth in representative claim 1, with the exception of the use of the NOESY-Assign process to determine the three dimensional structure of the unknown protein. That is to say, with the exception of the use of the NOESY-Assign process, the claims do not distinguish the appellants' method over the method taught by Wallace. To the extent that the appellants might be arguing that Wallace does not disclose the same sequence of steps as set forth in said claim, we point out that absent evidence to the contrary, the

order in which said steps are performed does not render the claimed method obvious over the applied prior art. In re Burhans, 154 F.2d 690, 692, 69 USPQ 330, 332 (CCPA 1946). Thus, we find that the method set forth in representative claim 1 would have been obvious to one of ordinary skill in the art over the teachings of Wallace which discloses first the characterization of a protein domain of known function and then the comparison of the three dimensional structure of the known protein with the three-dimensional structures of unknown proteins in a protein database. Wallace, e.g., the abstract. We further find that the teachings of Mumenthaler as to a more highly efficient method of automatically calculating the three-dimensional structure from an NMR spectra, would have motivated said person to use the automated analysis of the NMR spectra using a NOESY-Assign process in the method disclosed by Wallace.

Second, contrary to the appellants' arguments, we find that Wallace teaches the identification of a protein that folds into a stable domain with a defined three-dimensional structure. Attention is directed to the triad disclosed by Wallace which defines a protein domain comprising Ser195-His57-Asp102. Wallace p. 1004, col. 1, last para. The "triad" forms a stable domain having a defined three-dimensional structure. Id., p. 1005, col. 1, second para. Wallace employs said three-dimensional structure as a functional template to identify other "triads" having the same function from a set of enzyme and non-enzyme proteins. Id., p. 1009, col. 2; Figure 5; Table 2. Thus, we find that Wallace's teaching of comparing a protein domain having a known catalytic function which comprises a triad of three specific amino acids; viz.; Ser, His

and Asp, to identify new protein structures having the same function is no different from the claimed invention. The triad taught by Wallace is present in the domain of a protein having a known function and the three-dimensional structure of said domain is compared with other protein domains of unknown function to determine their biological function.

. Third, we do not find that the teachings of Wallace are limited to finding only the biochemical function of unknown proteins which have the Ser-His-Asp triad. Wallace discloses that the data suggest "the development of databases of 3D templates, such as those that currently exist for protein sequence templates, will help identify the functions of new protein structures [i.e., 3-D structures] as they are determined and pinpoint their functionally important regions." Wallace, the abstract. Thus, as discussed above, we find that the teachings of Wallace, and Mumenthaler, would have suggested the claimed method to those having ordinary skill in the art at the time the application was filed.

The appellants argue that Wallace does not teach or suggest to one of ordinary skill in the art "to take a single- or multi-domain protein or polypeptide of unknown function and identify each individual domain of said protein or polypeptide" as set forth in claim 13. Brief, p. 16. We find this argument unconvincing.

First, as discussed above, the appellants have stated that the claims stand or fall together. Brief, p. 4. Thus, we need only consider the issue as they apply to representative claim 1.

Second, even if we assume, arguendo, that claim 13 is before us, we would still find the appellants' position untenable. That is, claim 13 is not directed to a method of identifying and determining the function of "each individual domain" of a multi-domain protein. Rather, said claim is directed to the identification of "at least one" polypeptide domain, expressing said domain, determining whether the expressed polypeptide can form a stable domain, etc. Thus, we do not find that the appellants arguments address a limitation present in the claims.

The appellants argue that Wallace and Mumenthaler do not teach the determination of the function of a protein of unknown function by determining the structure of the protein and then comparing said structure with the structures of known proteins in a database in order to identify homologous proteins. Brief, p. 21, see also the Reply Brief, pp. 2-3. We have addressed this argument on pages 13-15, above.

We note the appellants' argument in the Reply Brief, that "the pending claims are expressly limited to protein domains of preferably 50 to 300 amino acids in length." See, the Reply Brief, pp. 5-6. However, we point out that neither representative claim 1, nor claim 13, specifies the size of the protein domains recited therein. Accordingly, we find that this argument does not address a limitation present in the claim(s).

Accordingly, in view of the foregoing, Rejections II-VII are affirmed.

As a final matter, we point out that given our disposition of the case, claim 12 is now free of the prior art.

AFFIRMED-IN-PART

Joan Ellis
Administrative Patent Judge

Toni R. Scheiner
Administrative Patent Judge

Demetra J. Mills
Administrative Patent Judge

) BOARD OF PATENT
) APPEALS AND
) INTERFERENCES

JE/eld

Appeal No. 2005-0761
Application No. 09/744,002

Licata & Tyrrell P.C.
66 E. Main Street
Marlton, NJ 08053